(Translation)

Japanese Patent Kokai No. 40538/1997 (February 10, 1997)
Patent Application No. 214273/1995 (July 31, 1995)
Applicant: Lion Corporation
Inventor: T. Shimada
Agent: T. Kojima, Patent attorney

[Title of the invention]

Compositions for oral application

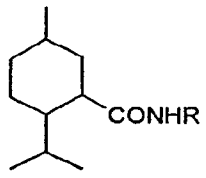
[Abstract]

[Problem to be solved]

There is provided a composition for oral application wherein palatability is secured, while maintaining a sensation to perceive a drug effect by a salicylic acid derivative and cinnamic aldehyde, and the whole of flavor may be enhanced together with an excellent storage stability.

[Means to solve the problem]

Concomitant use of a salicylic acid derivative and/or cinnamic aldehyde and an N-substituted-p-menthane-3-carboxamide represented by the following general formula (1).



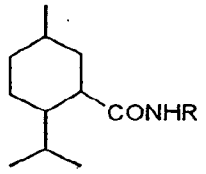
(1)

(wherein R is an alkyl group or an alkenyl group, each group having 1-10 carbon atoms).

[Claim for patent]

[Claim 1]

A composition for oral application which comprises a combination of a salicylic acid derivative and/or cinnamic aldehyde with an N-substituted-p-menthane-3-carboxamide represented by the following general formula (1)



(1)

(wherein R is an alkyl group or an alkenyl group, each group having 1-10 carbon atoms).

[Detailed explanation of the invention]

[Technical field to which the invention pertains]

This invention relates to a composition for oral application (hereinafter briefly referred to as an oral composition) wherein palatability is secured, while a sensation to perceive a drug effect by a salicylic acid derivative and cinnamic aldehyde is maintained, the whole of flavor is enhanced and storage stability is excellent.

[Prior art and the problem to be solved by the invention]

Salicylic acid derivatives have been widely used for the products for oral applications such as dentifrice, mouth refrigerant, mouth wash and the like, medicines, confectionery products such as chewing gum, candy, troche and the like, cosmetics, soaps and others, and they are blended for potentiating a pharmacological effect or a sensation to perceive a drug effect by flavoring compounds in those flavored products, sweetening the products or enhancing the smell or taste of flavoring compounds.

However, although salicylic acid derivatives when blended into the products could be percutaneously absorbed through the skin or oral cavity membrane to exert a pharmacological effect such as an analgesic effect, these derivatives have disadvantages in that they may be easily decomposed to show a poor storage stability and they have their own extremely strong and peculiar smell and heavy sweetness.

On the other hand, cinnamic aldehyde has also been widely used for the edible products, medicines, confectionery products and others and blended for the purpose of exerting a pharmacological effect, a sensation to perceive a drug effect or an accentuated feeling as flavors or of sweetening. The cinnamic aldehyde when blended into the products could also show effects such as an antifungal activity, a hemolytic activity, a cardiac depression activity, an activity on central nervous system, e.g., a sedative activity or a body temperature depression activity, or a choleretic activity, but cinnamic aldehyde has disadvantages in that it tends to be easily colored in itself and has a peculiar smell and a heavy sweetness.

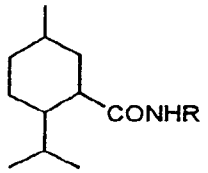
Accordingly, when a salicylic acid derivative and cinnamic aldehyde are individually blended alone or in combination therewith, the problem of storage stability such as coloration of the products or separation of liquid phases in the products may be readily presented and it is difficult to secure palatability owing to their peculiar smell or heavy sweetness (See, the Pharmacopoeia of Japan and other related reference materials). Accordingly, an amount of the salicylic acid derivative or cinnamic aldehyde to be blended to the edible products has been naturally restricted and various studies have been hitherto made in order to secure palatability while providing a pharmacological effect or a sensation to perceive a drug effect by both compounds or to

maintain storage stability. However, it may be said that satisfactory results could not have been obtained yet.

This invention has been made in view of the above circumstances, and it is the object of this invention to provide an oral composition which may secure palatability while providing a pharmacological effect or a sensation to perceive a drug effect by both compounds and enhance the whole of flavor and further have an excellent storage stability.

[Means to solve the problem and embodiments of the invention]

We have made extensive and earnest studies to achieve the above-mentioned object and, as a result, found that an oral composition comprising a salicylic acid derivative and/or cinnamic aldehyde can secure palatability, while maintaining a sensation to perceive a drug effect by the salicylic acid derivative and/or cinnamic aldehyde, and unexpectedly enhance the whole of flavor and further have an excellent storage stability without any decomposition of the salicylic acid derivative or any coloration or liquid phase separation caused by cinnamic aldehyde, by blending a N-substituted-p-menthane-3-carboxamide having the following general formula (1) into the said composition. This invention has been completed upon this finding.



(1)

(wherein R is an alkyl group or an alkenyl group, each group having 1-10 carbon atoms).

In accordance with this invention, there is provided an oral composition which comprises a combination of

a salicylic acid derivative and/or cinnamic aldehyde with an N-substituted-p-menthane-3-carboxamide represented by the above general formula (1).

This invention will be explained in greater detail hereinbelow.

The oral composition of this invention may be prepared in the form of, for example, dentifrice, mouth wash, mouth refrigerant, chewing gum, candy, troche, soft drink, etc. and comprises a salicylic acid derivative and/or cinnamic aldehyde and an N-substituted-p-menthane-3-carboxamide.

As the salicylic acid derivatives which may be used in this invention, there may be preferably used, for example, methyl salicylate or ethyl salicylate.

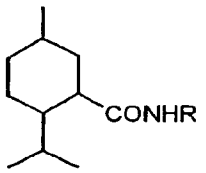
The salicylic acid derivatives may be any of those which may be isolated from essential oils of plant and other sources or may be synthesized, while there may be also used those essential oils in themselves, which contain the salicylic acid derivatives, such as wintergreen oil, sweet birch oil, ylang ylang oil, rue oil, clove oil, wormwood oil, tuberose flower oil, ocotea oil and the like.

The cinnamic aldehyde which may be used in this invention may be any of those which may be isolated from essential oils of plant and other sources or may be synthesized, while there may be also used those essential oils in themselves, which contain cinnamic aldehyde, such as cassia, cinnamon, lemon palm oil and the like.

In this invention, there may be individually used any one compound selected from the said salicylic acid derivatives and cinnamic aldehyde or any combination of two or more thereof. An amount thereof to be blended may be preferably 0.01-0.4% (percent by weight: The same shall apply hereafter, unless otherwise indicated.), particularly, 0.05-0.3%, upon the total composition. If the blended amount is less than 0.01%, a sufficient sensation to perceive a drug

effect or sweetness could not be achieved in some cases, while, if more than 0.4%, there could not be secured palatability in some cases owing to a peculiar smell or a heavy sweetness of the salicylic acid derivative or cinnamic aldehyde.

The N-substituted-p-menthane-3-carboxamide which may be used in this invention is represented by the following general formula (1)



(1)

(wherein R is an alkyl group or an alkenyl group, each group having 1-10 carbon atoms, preferably 1-4 carbon atoms).

In the above general formula (1), R may be, for example, an alkyl group such as a methyl group, an ethyl group, a n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group and the like, and an alkenyl group such as an ethenyl group, a propenyl group or a butenyl group. In particular, an ethyl group, an n-propyl group and an isopropyl group may be preferable.

Of the N-substituted-p-menthane-3-carboxamides of the above general formula (1), there may be preferably used in this invention N-ethyl-p-menthane-3-carboxamide in view of its excellent effect to improve palatability.

An amount of the N-substituted-p-menthane-3-carboxamide of the above general formula (1) to be blended is preferably 0.01-1%, in particular, 0.05-0.5%, upon the total composition. If the blended amount is less than 0.01%, satisfactory results could not be achieved in some cases, while, if more than 0.1%, there may be given a poor feeling in use.

Into the present oral composition may be incorporated other optional components other than the above essential ingredients in accordance with the dosage form adopted. Specifically stated, in the case of dentifrices, there may be blended a polishing agent, a binder and a thickening agent according to a conventional manner and, further, there may be blended as an additional active ingredient one or more of an enzyme such as dextranase, amylase, protease, lysozyme, lytic enzyme, etc., a fluorine compound such as sodium monofluorophosphate, sodium fluoride, stannic fluoride, etc., a chlorhexidine salt, ε-aminocaproic acid, aluminum chlorohydroxy allantoinate, dihydrochlesterol, a glycyrrhetic acid salt, sodium chloride, benzethonium chloride, a water-soluble phosphoric acid compound such as potassium or sodium orthophosphate, etc., azulene, vitamins and the like. As a surface active agent, there may be incorporated one or more of an anionic surface active agent such as sodium lauryl sulfate, lauroylsarcosinate, α-olifinsulfonate, taurate, lauryl monoglyceride sulfate, lauryl monoglyceride sulfonate, an N-long chained acyl amino acid, soap and the like; a nonionic surface active agent such as lauric acid diethanolamide, stearyl monoglyceride, sucrose fatty acid ester, lactose fatty acid ester, poly(oxyethylene)sorbitan monostearate, etc., an amphoteric surface active agent such as a polyglycerol fatty acid ester, a betaine-type or amino acid-type surface active agent, etc.; and the like (usually, a blended amount of 0.1-3%). And further, there may be also incorporated a sweetening agent such as saccharin sodium, stevioside, neohesperidin dihydrochalcone, thaumatin, glycyrrhizin, perillartine, etc., an antiseptic agent such as a p-hydroxybenzoic acid ester, sodium benzoate, etc., and other components, and the desired components as above may be prepared by kneading with a proper amount of water. An amount of the above active ingredient to

be blended may be in any usual range unless the effect of this invention is prevented.

[Effect of the invention]

The oral composition according to this invention can may secure palatability, while maintaining a sensation to perceive a drug effect by a salicylic acid derivative and cinnamic aldehyde, and enhance the whole of flavor and further have an excellent storage stability, such that it may be widely used for dentifrice, mouth wash, mouth refrigerant, chewing gum, candy, troche, soft drink and the like.

[Examples]

This invention will be specifically explained by way of the test examples and examples as shown below, but this invention is not to be limited to the following examples. Unless otherwise indicated, all parts in these examples are given by weight.

[Test Example 1]

Oral compositions of No. 1 series having the following compositions were prepared using those flavoring compositions as shown in Tables 1-3 and then subjected to the following sensory evaluation by 10 professional panelists. The results are shown in Tables 1-3.

Anhydrous silicic acid	30.0%
Glycerol solution(80%)	30.0
Polyethylene glycol	2.0
Carboxymethylcellulose sodium	1.2
Sodium lauryl sulfate	1.5
Flavoring composition shown in Tables 1-3	1.0
Saccharin sodium	0.1
Purified water	34.2
Total	100.0%

Sensory evaluation:

Sensation to perceive drug effect, palatability and enhancement in flavor:

◎ : Potent combined effect observed by blending methyl salicylate and/or cinnamic aldehyde

○ : Combined effect observed

X : No combined effect observed

Storage stability (evaluated after storage at 40℃ over one month)

◎ : No discoloration, separation and other observed

○ : Discoloration, separation and others hardly observed

X : Discoloration, separation and others observed

General evaluation:

○ : Good quality as generally evaluated

X : Poor quality as generally evaluated

It can be seen from the results of Tables 1-3 that blending of either or both of the salicylic acid derivative and/or cinnamic aldehyde could provide a sensation to perceive a drug effect, but all of palatability, storage stability and effect of enhancing flavor could not be satisfied as a whole.

[Table 1]

No.	1-1	1-2	1-3	1-4	1-5	1-6
Methyl salicylate	1	5	15	30	40	50
Peppermint oil	50	50	50	50	50	50
Ethanol	R*	R	R	R	R	-
Total(%)	100	100	100	100	100	100
Sensation to perceive drug effect	X	X	○	◎	◎	◎

Palatability	◎	○	X	X	X	X
Storage stability	○	○	○	X	X	X
Enhanced flavor	○	○	○	X	X	X
General evaluation	X	△	X	X	X	X

R* : Remainder(The same will be similarly applied hereafter.)

[Table 2]

No.	1-7	1-8	1-9	1-10	1-11	1-12
Cinnamic aldehyde	1	5	15	30	40	50
Peppermint oil	50	50	50	50	50	50
Ethanol	R	R	R	R	R	-
Total(%)	100	100	100	100	100	100
Sensation to perceive drug effect	X	○	○	○	○	○
Palatability	◎	○	○	X	X	X
Storage stability	○	○	X	X	X	X
Enhanced flavor	○	X	X	X	X	X
General evaluation	X	X	X	X	X	X

[Table 3]

No.	1-13	1-14	1-15	1-16	1-17	1-18
Methyl salicylate	0.5	2.5	10	15	20	25
Cinnamic aldehyde	0.5	2.5	10	15	20	25
Peppermint oil	50	50	50	50	50	50
Ethanol	R	R	R	R	R	-
Total(%)	100	100	100	100	100	100
Sensation to perceive drug effect	○	◎	◎	○	○	○
Palatability	○	○	X	X	X	X
Storage stability	○	○	X	X	X	X

Enhanced flavor	X	X	X	X	X	X
General evaluation	X	X	X	X	X	X

[Test Example 2]

Oral composition of No. 2 having the following compositions was prepared using the flavoring composition of Test Example 1, No. 1-15 together with additional flavoring materials as shown in Table 4 and then subjected to the sensory evaluation using the following standards. The results are shown in Table 4.

Composition of oral composition No. 2

Aluminum hydroxide	40.0%
Glycerol solution(80%)	5.0
Sorbitol solution(60%)	20.0
Carrageenan	0.2
Propylene glycol	5.0
Sodium lauryl sulfate	1.2
Carboxymethylcellulose sodium	1.5
Titanium oxide	0.3
Sodium benzoate	0.1
Methyl p-hydroxybenzoate	0.1
Saccharin sodium	0.1
Flavoring composition No. 1-15	1.0
Additional flavoring material A-E*	0.1
Purified water	Remainder
Total	100.0%

* : One of the additional flavoring materials A-E as shown in Table 4

Evaluation standards:

◎ : Potent combined effect observed
○ : Combined effect observed
△ : Slight combined effect observed
X : No combined effect observed

It has been confirmed from the results of Table 4 that palatability can be significantly improved by blending N-ethyl-p-menthane-3-carboxamide.

[Table 4]

Mark	Additional flavoring material	Evaluation result
A	Menthol	○
B	Anethole	X
C	Carvone	X
D	Cineole	X
E	N-Ethyl-p-menthane-3-carboxamide	◎

[Test Example 3]

The same oral compositions of No. 2 series as described in Test Example 2 were blended with the flavoring composition as shown in Test Example 1 and N-ethyl-p-menthane-3-carboxamide as shown in the following Table 5 and then subjected to the sensory evaluation using the above-defined evaluation standards shown in Table 4. The results are shown in Table 5. It can be seen from the results of Table 5 that the oral composition with satisfactory drug effect sensation, palatability and enhanced flavor can be obtained by blending N-ethyl-p-menthane-3-carboxamide in the range of 0.01-1% upon the total composition.

[Table 5]

No.	3-1	3-2	3-3	3-4	3-5	3-6
Oral composition No.2*	97.0	97.0	97.0	97.0	97.0	97.0
Flavoring composition No. 1-15	1.0	1.0	1.0	1.0	1.0	1.0
N-Ethyl-p-menthane-3-carboxamide	0.01	0.05	0.1	0.5	1.0	2.0

Purified water	R	R	R	R	R	-
Total(%)	100	100	100	100	100	100
Sensation to perceive drug effect	○	◎	◎	◎	◎	◎
Palatability	△	◎	○	◎	◎	◎
Storage stability	X	○	◎	○	○	○
Enhanced flavor	△	○	◎	◎	◎	○
General evaluation	△	◎	◎	◎	○	X

* : The same composition as the flavoring composition No. 2 except that the flavoring composition No. 1-15 (1.0%), the additional flavoring material A-E and a part of the purified water (1.9%) were excluded

[Test Example 4]

In order to evaluate the effects by the addition of N-ethyl-p-menthane-3-carboxamide, compositions were prepared by adding N-ethyl-p-menthane-3-carboxamide to each of the oral compositions No.1 series of Test Example 1 at 0.5%, and the effects by this combination were evaluated upon the following standards, as compared with the original edible composition without blending the said carboxamide. The results are shown in Tables 6-8.

Evaluation standards:

◎ : Potent combined effect observed

○ : Combined effect observed

X : No combined effect observed

It has been confirmed from the results of Tables 6-8 that a sensation to perceive a drug effect, palatability, storage stability and enhanced flavor can be improved by a concomitant use of a salicylic acid derivative and/or cinnamic aldehyde and an N-substituted-p-menthane-3-carboxamide.

[Table 6]

No.	4-1	4-2	4-3	4-4	4-5	4-6
Oral composition of Test Example 1	1-1	1-2	1-3	1-4	1-5	1-6
Sensation to perceive drug effect	○	○	◎	◎	◎	◎
Palatability	◎	◎	○	○	○	X
Storage stability	○	○	○	○	○	X
Enhanced flavor	○	◎	◎	○	○	○
General evaluation	○	◎	◎	○	○	X

[Table 7]

No.	4-7	4-8	4-9	4-10	4-11	4-12
Oral composition of Test Example 1	1-7	1-8	1-9	1-10	1-11	1-12
Sensation to perceive drug effect	○	○	◎	◎	○	○
Palatability	◎	◎	◎	○	○	X
Storage stability	○	○	○	○	○	X
Enhanced flavor	○	◎	◎	◎	○	○
General evaluation	○	◎	◎	◎	○	X

[Table 8]

No.	4-13	4-14	4-15	4-16	4-17	4-18
Oral composition of Test Example 1	1-13	1-14	1-15	1-16	1-17	1-18
Sensation to perceive drug effect	○	○	◎	◎	○	○
Palatability	○	◎	○	○	○	○
Storage stability	○	○	○	○	○	X
Enhanced flavor	○	◎	◎	◎	○	○
General evaluation	○	◎	◎	◎	○	X

[Example 1] Toothpaste

Dibasic calcium phosphate.dihydrate	10%
Zeolite	10
Sorbitol solution(60%)	20
Sodium lauryl sulfate	1.5
Carrageenan	0.5
Polyethylene glycol	1.0
Titanium oxide	0.1
Saccharin sodium	0.1
Peppermint oil	0.2
Menthol	0.3
Cinnamic aldehyde	0.2
Methyl salicylate	0.05
Ethyl salicylate	0.02
M-Ethyl-p-menthane-3-carboxamide	0.3
Anethole	0.1
Fruit flavors	0.05
Purified water	Remainder
Total	100.0%

[Example 2] Liquid dentifrice

Zirconium-binding silicate	10%
Precipitated silica	10
Glycerol solution(80%)	40
Xanthane gum	0.2
Sodium lauryl sulfate	1.5
Sodium polyacrylate	2.5
Propylene glycol	1.0
Sodium fluoride	0.2
Saccharin sodium	0.2
Menthol	0.4
Spearmint oil	0.05

Methyl salicylate	0.2
N-Butyl-p-menthane-3-carboxamide	0.5
Lemon oil	0.2
Anise oil	0.1
Cardamom Orange	0.05
Brilliant Blue	Minor amount
Purified water	Remainder
Total	100.0%

[Example 3] Mouth wash

Citric acid	0.2%
Sodium citrate	0.2
Glycerol solution(85%)	10.0
Ethanol(95%)	10.0
Menthol	0.1
Peppermint oil	0.01
Spearmint oil	0.005
Cinnamic aldehyde	0.02
N-Ethyl-p-menthane-3-carboxamide	0.05
Cetylpyridinium chloride	0.05
Purified water	Remainder
Total	100.0%

[Example 4] Chewing gum

Chewing gum base	45.0%
Malt syrup	10.0
Powder sugar	40.0
Peppermint oil	0.1
Menthol	0.1
Methyl salicylate	0.1
N-Isopropyl-p-menthane-3-carboxamide	0.1

Palatinose	1.0
Purified water	Remainder
Total	100.0%

[Example 5] Liquid mouth refrigerant

Ethanol	45.0%
Polyoxyethylene hardened castor oil	2.0
Sorbitol solution(60%)	30.0
Peppermint oil	0.5
Menthol	0.5
Methyl salicylate	0.1
N-Ethyl-p-menthane-3-carboxamide	1.0
Anise oil	0.2
Purified water	Remainder
Total	100.0%